REMARKS

Claims 1-9 and 11 are currently pending. Claim 12 has been withdrawn without prejudice. Claims 10 and 13-36 have been previously cancelled without prejudice. Reconsideration is respectfully requested for the reasons noted below.

No new matter is introduced.

Rejection under 35 USC § 112, Second Paragraph

Claims 1-9 and 11 are rejected under 35 USC § 112, second paragraph, for the reasons noted at page 2 of the Office Action. In particular, the Office Action asserts that it cannot be understood how the chip can be "configured to be inserted and removed from the measuring apparatus" because the "measuring apparatus" is recited as part of the chip.

In response, to expedite prosecution, Applicants amend claim 1 to delete[1] the "measuring apparatus" language as follows:

> 1. (CURRENTLY AMENDED) A gene detecting chip to detect and to analyze at least one of genes, single base substitution SNP or point mutation of genes, the gene detecting chip comprising:
>
> a body having a depression;
>
> ~~an upper~~a cover ~~to be fixed to said body from above~~over said depression;
>
> an enclosed internal space ~~part,~~ formed ~~by~~ between said depression ~~in said body as a result of~~ and said ~~upper~~ cover ~~being fixed to said body, capable of being filled with and being emptied of~~ to receive gene samples;
>
> a plurality of measuring electrodes configured to measure an electric current variation between the measuring electrodes and a common electrode, the measuring electrodes formed at ~~the~~ a bottom of said space ~~part~~,
>
> wherein one of a plurality of PCR products or oligonucleotides is immobilized on one of said plurality of measuring electrodes and said electric current variation corresponding to hybridization with said PCR products or oligonucleotides is sufficient to detect point mutations,
>
> ~~a~~ wherein the common electrode ~~which~~ is a counter electrode to said

[1] Underlining indicates currently added text and ~~strikethrough~~ indicates currently removed text.

measuring electrodes arranged in the space ~~part~~; and

~~a measuring apparatus capable of detecting and analyzing genes,~~

wherein, when a voltage is applied between said common electrode and said measuring electrodes ~~to detect a gene~~, the electric current variation between said common electrode and said measuring electrode can be detected~~, and~~

~~when the chip is configured to be inserted into and removed from the measuring apparatus, and is configured to be electrically connected to said measuring apparatus to detect at least one of genes, single base substitution SNPP or point mutation of genes by detecting electric currents between said counter electrode and each of said plurality of measuring electrodes, wherein the at least one of the genes, single base substitution SNP or point mutation of genes is obtained by placing gene sample, nucleic acid sequence samples or gene-amplified nucleic acid sequence samples in the space part to form double strands with a plurality of PCR products or oligonucleotides, placing an electrolye including an electrochemically active molecule in the space part; controlling the temperature at which said double strands are formed, removing the chip from the measuring apparatus, washing, and injecting electrolytic solution including electrochemically active molecules into the space part before detecting electric currents~~.

In view of the removal of the "measuring apparatus" language, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-9 and 11 under 35 USC § 112, second paragraph.

Rejection Under 35 USC § 102(b)

Claims 1 and 4-9 are rejected under 35 USC § 102(b) as being anticipated by U.S. Pat. No. 5,632,957 to Heller et al. (hereinafter "Heller") for the reasons noted at pages 3-5 of the Final Office Action. In particular, the Office Action asserts that all the features of these rejected claims are disclosed by Heller.

In response, to expedite prosecution, Applicants have amended claim 1 to further recite "a plurality of measuring electrodes configured to measure an electric current variation between the measuring electrodes and a common electrode" and also to recite "wherein one of a plurality of PCR products or oligonucleotides is immobilized on one of said plurality of measuring electrodes and said electric current variation corresponding to hybridization with said PCR products or oligonucleotides is sufficient to detect point mutations." (Emphasis added.)

The claimed chip is "configured to measure [the] electric current variation" as noted in

amended claim 1 herein. (Emphasis added.) In other words, the claim permits the actual "electric current variation" to be quantified by, for example, a "measuring apparatus 3" as illustrated in Fig. 1 of the specification originally filed.

Deficiencies of Heller

In comparison to amended claim 1, Heller does not disclose nor teach **(1)** any PCR products or oligonucleotides immobilized to the measuring electrodes themselves, **(2)** that the plurality of measuring electrodes are configured to measure an electric current variation between the measuring electrodes and a common electrode, and/or **(3)** that the measured electric current variation (between the measuring electrodes and the common electrode) is sufficient to detect point mutations of gene segments hybridized to the PCR products or oligonucleotides immobilized on the measuring electrodes.

For example, FIGS. 2A and 2B (of Heller) indicate that oligonucleotides or PCR products are not immobilized on the electrodes thereof as further explained below. In particular, FIGS. 2A and 2B (of Heller) are reproduced below together with relevant text relating to the same:

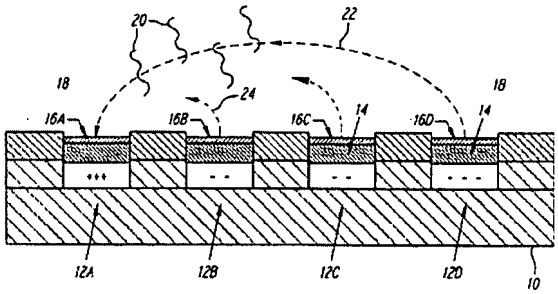

FIG. 2A

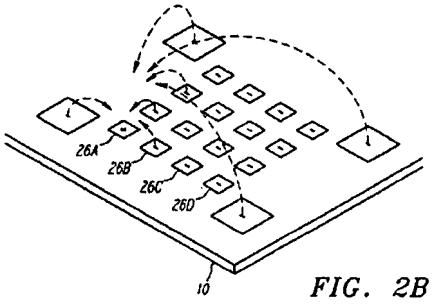

FIG. 2B

The relevant text relating to FIGS. 2A and 2B (of Heller) clearly indicates that electrodes 12A (of FIG. 2A) and 26A (of FIG. 2B) are positively charged while the remaining electrodes 12B, 12C and 12D (of FIG. 2A) and remaining electrodes including 26B, 26C and 26D (of FIG. 2B) are negatively charged to promote **migration** of non-immobilized DNA fragments 20 (having a net negative charge) **from** the **negative** electrode sites **toward** the **positive** electrode site along electrophoretic lines of force 22 and 24:

> Charged entities 20, such as charged DNA are located within the reservoir 18. In one aspect of this invention, the active, programmable, matrix system comprises a method for transporting the charged material 20 to any of the specific microlocations 12. When activated, a microlocation 12 generates the free field electrophoretic transport of any charged functionalized specific binding entity 20 towards the electrode 12. For example, if the electrode 12A were made positive and the electrode 12D negative, electrophoretic lines of force 22 would run between the electrodes 12A and 12D. The lines of electrophoretic force 22 cause transport of charged binding entities 20 that have a net negative charge toward the positive electrode 12A. Charged materials 20 having a net positive charge move under the electrophoretic force toward the negatively charged electrode 12D. When the net negatively charged binding entity 20 that has been functionalized contacts the attachment layer 16A as a result of its movement under the electrophoretic force, the functionalized specific binding entity 20 becomes covalently attached to the attachment layer 16A. [(Heller at col. 8, lines 20 – 40; emphasis added.)]
>
> * * *
>
> The electrophoretic force lines 24 serve to drive away negatively charged binding entities 20 from the attachment layer 16B and towards the attachment layer 16A. [(Heller at col. 8, lines 46 – 49; emphasis added.)]

Certainly, in view of the above-noted migration of the fragments of material 20, such fragments are not immobilized on the electrodes because, if the fragments of material 20 were immobilized, then such fragments of material 20 would not be free to migrate as noted in Heller.

Also, there is no disclosure (in Heller) that PCR products or oligonucleotides are immobilized on the electrodes 12A, 12B, 12C, or 12D of FIG. 2A (of Heller). To the contrary, FIG. 2A (of Heller) illustrates that the actual electrodes 12A, 12B, 12C and 12D are buried below the

permeation layer 14. Therefore, such configuration (of Heller) makes it impossible to immobilize PCR products or oligonucleotides on the electrodes (of Heller) themselves. This function of the permeation layer 14 is described in relevant part below in Heller:

> Generally, a substrate 10 supports a matrix or array of electronically addressable microlocations 12. For ease of explanation, the various microlocations in FIG. 2A have been labelled 12A, 12B, 12C and 12D. A **permeation layer 14 is disposed above the individual electrodes 12**. The **permeation layer** permits transport of relatively small charged entities through it, but **precludes large charged entities, such as DNA, from contacting the electrodes 12 directly**. The **permeation layer 14 avoids the electrochemical degradation which would occur in the DNA by direct contact with the electrodes 12**. It further **serves to avoid the strong, non-specific adsorption of DNA to electrodes**. [(Heller at col. 8, lines 1 – 13; emphasis added.)]

Heller clearly describes that the "permeation layer . . . precludes large charged entities, such as DNA, from contacting the electrodes 12." (Emphasis added.) Heller also clearly describes that the "permeation layer 14 avoids the electrochemical degradation which would occur in the DNA by direct contact with the electrodes 12" as noted above. (Emphasis added.) Thus, it is unambiguously clear that, pursuant to the disclosure of Heller, no PCR products or oligonucleotides are "immobilized on the electrodes" as recited in amended claim 1 (*e.g.*, ". . . wherein one of a plurality of PCR products or oligonucleotides is immobilized on one of said plurality of measuring electrodes . . . ."). (Emphasis added.) That point is further emphasized in Heller by the statements:

> An oxidized capture probe with a fluorescent marker attached was attracted to the surface of the permeation layer at a micro-location by electrophoretic transport. The permeation layer was removed from the micro-location by mechanical means. No evidence of the presence of the fluorescently labeled capture probe was observed. **This demonstrates the ability of the permeation layer [14] to protect the DNA from the electrode surface**. [(Heller at col. 8, lines 16 – 24; emphasis added.)]

With regard to the method of detection of hybridization, Heller describes in some detail the use of fluorescence rather than the "plurality of measuring electrodes configured to measure an

electric current variation between the measuring electrodes and a common electrode . . . wherein . . . said electric current variation corresponding to hybridization with said PCR products or oligonucleotides is sufficient to detect point mutations" as recited in amended claim 1. While other detection methods are disclosed in Heller, no sufficient detail regarding measurement of electric current variation (as recited in amended claim 1) is taught, or disclosed by Heller.

Support for the above noted claim amendments is provided in Table 1 of the specification (originally filed) where a dA20 segment is hybridized with the immobilized probes **(a)** dT20, **(b)** dT10dAdT9, **(c)** dT8dA4dT8, **(d)** dAdT19, **(e)** dA3dT17, **(f)** dT19dA and **(g)** dT17dA3 noting that the end(s) of probes **(a)**, **(b)** and **(c)** are complimentary (*i.e.*, matched) to dA20 while the end(s) of probes **(d)**, **(e)**, **(f)** and **(g)** are not complimentary (*i.e.*, mismatched) to dA20.

Bearing the foregoing in mind, the data presented in Table 1 of the specification originally filed illustrates that point mutations are easily detected by the measured electric current variation in view of the critical point (noted in the specification originally filed):

> Particularly, when the terminal parts [*i.e.*, ends] of the sequences are mismatched, current variations greater than that [*i.e.*, variation] of the Tm value were observed. [Specification originally filed at page 18, lines 24-26; emphasis added.)]

The foregoing statement is corroborated by the data presented in Table 1 (see page 18, lines 16-21) of the specification originally filed:

Table 1[2]

	dT20	dT10dAdT9	dT8dA4dT8	dAdT19	[d]A3dT17	dT19dA	dT17dA3
Current variation (%)	37	22	15	14	14	20	12
Tm (°C)	46	36	21	45	46	42	41
ΔTm (°C)	n/a	46 – 36 = 10	46 – 21 = 25	46 – 45 = 1	46 – 46 = 0	46 – 42 = 4	46 – 41 = 5
Tm variation calculation	n/a	(10/46) x 100 =	(25/46) x 100 =	(1/46) x 100 =	(0/46) x 100 =	(4/46) x 100 =	(5/46) X 100 =
Tm variation (%)	n/a	21.74	54.35	1.18	0	8.70	10.87
Mismatch at terminal end	No	No	No	Yes	Yes	Yes	Yes

[2] Last four rows (gray) added for detailed comparison. Bold and gray emphasis added.

In view of the data presented in Table 1 of the specification originally filed, it is possible to detect point mutations of the hybridized segment. Such detection with electric current variation detection also greatly improves throughput detection of point mutations because the entire gene segment sequence does not have to be fully identified (*i.e.*, fully sequenced) to determine if a point mutation exists. Such capability is not taught or disclosed by Heller.

Furthermore, rather than using electric current variation measurements (as recited in amended claim 1), Heller relies on the use of optical methods to detect hybridization as noted therein in relevant part with reference to FIG. 7 thereof:

> The controller computer 80 optionally controls the illumination source 94 for excitation of fluorescence to detect DNA hybridization. In the preferred embodiment, the illumination source 94 is a laser which outputs radiation at an appropriate wavelength to excite fluorescent markers included within the APEX system 92. [Heller col. 13, lines 60 - 65; emphasis added.)]
>
> The output of the APEX system 92 is passed through observation path 96 to the detector 98. The observation path 96 may be a physical connection, such as through a fiber optic, or may comprise an optical path such as through a microscope. Optical filters may be utilized in the observation path to reduce illumination of the detector at wavelengths not corresponding to the emission spectra of the fluorescent markers in the APEX system 92. [Heller from col. 13, line 66 to col. 14, line 6; emphasis added.)]

Thus, in view of the above-noted deficiencies (of Heller noted in points **(1)**, **(2)**, and **(3)** above), amended claim 1 is patentably distinguished (*i.e.*, novel) over Heller. As such, Applicants respectfully submit that amended claim 1 and claims 4-9 ultimately depending from claim 1 overcome the anticipation rejection under 35 USC § 102(b) over Heller. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, and 4-9 under 35 U.S.C. § 102(b) over Heller.

Rejection Under 35 USC § 103(a)

Claims 1 – 3 and 11 are rejected under 35 USC § 103(a) as being obvious over Heller in view of U.S. Pat. No. 5,587,128 to Wilding et al. (hereinafter "Wilding") for the reasons noted at

pages 6-9 of the Office Action. Applicants incorporate by reference herein (and apply) their above-noted remarks regarding the deficiencies of Heller without having to repeat the same.

With regard to claim 1, Applicants respectfully submit that the Office Action does not clearly articulate the basis for its obviousness rejection. Presumably, the reasoning applied under 35 USC § 102(b) (*i.e.,* novelty) is now applied under 35 USC § 103(a) (*i.e.*, obviousness).

With regard to claim 2 reciting injection holes, the Office Action asserts (at page 7, lines 19-20 and at the sentence bridging pages 7 – 8 of the Office Action) that while Heller does not disclose injection holes extending to the depression of the body, Wilding does so.

With regard to claim 3 reciting a transparent cover, the Office Action asserts that while Heller does not disclose a transparent cover, Wilding does so. See Office Action at page 8, lines 16 – 17 and 22 – 23.

With regard to claim 11 reciting peltier devices, the Office Action asserts that while Heller does not disclose peltier devices, Wilding does so. See Office Action at page 9, lines 7 – 8 and 13 – 15.

We note that each of claims 2, 3, and 11 ultimately depend on claim 1 (as amended). Thus, in response, Applicants respectfully point out that by their dependency, claims 2, 3 and 11 incorporate the amendments of claim 1. Therefore, Applicants respectfully further point out that the disclosure of Wilding does not rectify the above-noted deficiencies (of Heller) indicated in reference to the rejections under 35 USC § 102(b). Thus, even if combined with Wilding, the combination of Heller and Wilding does not arrive at the claimed invention of amended claim 1 and that of claims 2, 3, and 11 depending therefrom.

Moreover, Heller in view of Wilding does not disclose, teach or suggest Applicants' claimed invention (as amended) for the reasons noted above.

For at least these reasons, Applicants respectfully submit that claims 1-3 and 11 are patentable over Heller in view of Wilding. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3 and 11 under 35 U.S.C. § 103(a) over Heller in view of Wilding.

Non-statutory Obviousness-type Double Patenting Rejection

Claims 1 – 6, 8 and 11 are rejected under the non-statutory obviousness-type double patenting basis over claims 1 – 5, 7 and 16 – 22 of U.S. Pat. No. 6,916,614 to Takenaka et al. (hereinafter "Takenaka") in view of Wilding for the reasons noted at pages 10 – 11 of the Office Action.

Applicants will file a Terminal Disclaimer over Takenaka when all other grounds of rejection (if any) have been overcome or withdrawn.

CONCLUSION

Applicants respectfully submit that the claims (as amended) are patentable and request a written indication of the same.

If any issues remain to be resolved, the Examiner is earnestly requested to contact the undersigned attorney in order to promptly resolve any such issues and to expedite prosecution.

No fees are believed to be due. However, if any additional fees are required or an overpayment of fees made, please debit or credit our Deposit Account No. 19-3935, as needed.

Respectfully submitted,

STAAS & HALSEY LLP

Date: May 21, 2007
MONDAY.

By: Ajay Pathak
Ajay Pathak
Registration No. 38,266

1201 New York Ave, N.W., 7th Floor
Washington, D.C. 20005

Telephone: (202) 454-1594 (Direct)
(202) 434-1500 (Main)

Facsimile: (202) 434-1501

Enclosures:
RCE
Check for $910 (RCE fee of $790 and one-month EOT fee of $120)